Postgraduate Medical Journal (May 1979) **55**, 318–324

The respiratory response to pregnancy

J. A. MILNE
M.A., M.B., Ch.B., M.R.C.O.G.

Department of Obstetrics and Gynaecology, University of Cambridge

Summary

The respiratory response to pregnancy appears to be largely mediated by the action of progesterone and, perhaps to a lesser extent, oestrogens, at least in the first and second trimesters. The mechanical effects of the gravid uterus cause relatively little change in pulmonary mechanics, although finer changes in airways function require further investigation.

Dyspnoea during pregnancy is also probably hormone-mediated but the exact temporal relationship between hormone status, functional change and the development of symptoms is not yet clearly defined.

Introduction

The specialized changes in physiological function during normal pregnancy have aroused much interest and research, primarily on the organs of reproduction but also on several other organs and systems. Although some of these changes are well documented (Hytten and Leitch, 1971), this is not so of respiratory function in normal pregnancy (Woolcock and Read, 1972).

Many previous studies have employed measurement techniques with poor reproducibility and have studied small numbers of subjects at infrequent intervals throughout pregnancy. An attempt is now made to review what is known about changes in respiratory function during normal pregnancy, particularly in relation to the occurrence of dyspnoea and also the possible aetiological role of progesterone and oestrogens in these changes.

The role of the sex hormones in respiration

Progestogens

It was the demonstration of hyperventilation very early in gestation that first suggested that hormonal rather than mechanical factors might be involved (Hasselbach and Gammeltoft, 1915). Since that study, much evidence has accumulated to suggest that progesterone is responsible. It has been shown that ventilation is significantly greater in the luteal phase of the ovulatory cycle than the oestrogen-dominated follicular phase (England and Fahri, 1976; Milne, Pack and Coutts, 1977d), Fig. 1).

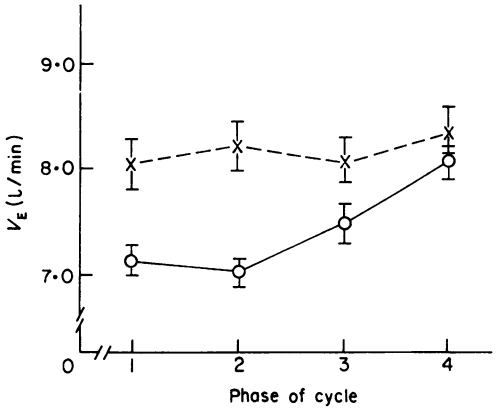

FIG. 1. Respiratory function during the menstrual cycle. Mean values for 2 groups of 10 subjects during menses (1), day 8–10 (2), day 14–16 (3) and day 25–30 (4). ×---× Taking oral contraceptives; O——O not taking oral contraceptives; bar indicates s.e. mean.

Furthermore, subjects taking an oral contraceptive preparation containing the progestogen, norethisterone, have a significantly greater minute ventilation than normal ovulatory subjects at all stages of their cycles, apart from late in the luteal phase (Fig. 1). This would seem to add weight to the case for a progestogen effect, although Tyler (1960) was unable to demonstrate a respiratory stimulant effect when norethisterone was administered parenterally to hypercapnic emphysematous subjects. When progesterone itself was substituted, however, ventilation increased.

This latter finding is well known because administration of progesterone to volunteers, both male and female (Goodland *et al.*, 1953) and to patients with chronic hypercapnic states (Lyons and Huang, 1968; Tyler, 1960) consistently increases ventilation and lowers alveolar carbon dioxide tension (P_{A,CO_2}).

Progesterone probably exerts its effect on ventilation by increasing the sensitivity of the respiratory centre to changes in P_{CO_2} (Lyons and Antonio, 1959).

0032-5473/79/0500-0318$02.00

Oestrogens

The effect of the oestrogens on the respiratory system is less well defined, although Goodland *et al.* (1953) have demonstrated in males that simultaneous administration of oestradiol can prolong, although not enhance, the hyperventilation caused by progesterone.

With respect to gas transfer across the alveolar-capillary membrane, Pecora, Putnam and Baum (1963) demonstrated a fall in pulmonary transfer factor (Tlco) for carbon monoxide after intravenous administration of the equine oestrogen, Premarin, to volunteers. It was postulated that this was caused by an increase in acid mucopolysaccharides in the alveolar-capillary membrane and thus an increased diffusion path. While there is also evidence of a fall in transfer factor during pregnancy, as will be discussed later, its relationship to oestrogen status is not so obvious (Milne *et al.*, 1977a).

In the light of this background knowledge of the role of the sex hormones in respiration, the respiratory function changes during normal pregnancy will now be discussed.

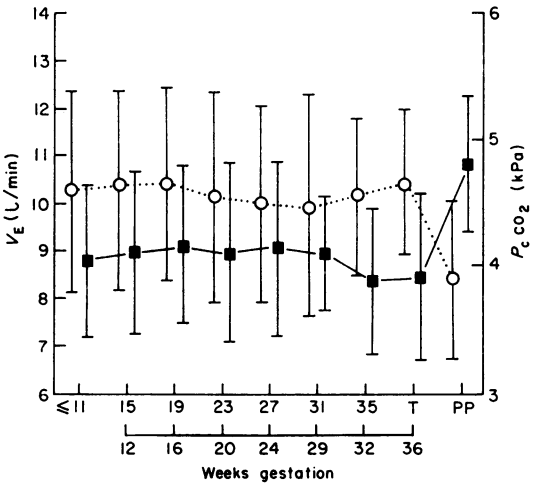

FIG. 2. Respiratory function during normal pregnancy and *post partum*. Mean values for minute ventilation (VE) ○ and capillary P_{CO_2} (P_cCO_2) ■. No.=31; T=term; PP=*post partum*.

Ventilation and gas exchange

Resting ventilation

There is almost universal agreement that a significant increase in resting minute ventilation takes place from very early on in pregnancy (Bonica, 1973). There is, however, considerable disagreement as to the time-course and, to a lesser extent, the magnitude of this increase. This results from lack of attention to attaining basal measurement conditions in many earlier studies (Plass and Oberst, 1938; Widlund, 1945) and to conclusions being drawn from the mean values of widely scattered results on small numbers of subjects (e.g. Pernoll *et al.*, 1975).

Previous studies have either shown a linear increase (of up to 40%) in ventilation and a consequent fall in P_{A,CO_2} throughout pregnancy (Widlund, 1945; Cugell *et al.*, 1953; Knuttgen and Emerson, 1974; Pernoll *et al.*, 1975) or a significant change in the first trimester which is maintained but not increased as pregnancy progresses (Bonica, 1973; Templeton and Kelman, 1976; Guzman and Caplan, 1974; Milne *et al.*, 1977b; Alaily and Carrol, 1978). In the Glasgow study of 31 subjects, a mean increase of 24% was demonstrated in resting minute ventilation (Fig. 2). This was established before the end of the first trimester but did not increase throughout pregnancy. This trend was mirrored by the fall in capillary P_{CO_2} (Fig. 2).

Most authors, however, seem agreed that the increase in ventilation is mediated by a raised tidal volume, respiratory frequency remaining constant (Bonica, 1973).

It may be that the failure of ventilation to increase after the first trimester can be explained in terms of the maternal respiratory response anticipating the ventilatory demands which later gestation will bring.

Gas transfer

In view of the increased volume of gas flowing in and out of the lungs during pregnancy, it is of interest now to consider how this is reflected in terms of gas transfer across the alveolar-capillary membrane.

While it is the transfer (or diffusion) of oxygen which is of concern during pregnancy, this process is relatively slow and its direct measurement is technically difficult. Carbon monoxide (CO) on the other hand, diffuses more easily, binds preferentially with haemoglobin, and its diffusing capacity can be readily measured (Ogilvie *et al.*, 1957). Any measurable decrease in carbon monoxide diffusing capacity will certainly indicate impairment of oxygen transfer.

There have been very few studies of pulmonary transfer factor (Tl) in normal pregnancy. Krumholz, Echt and Ross (1964) measured Tl twice, at 14 and 27 weeks' gestation, and found no difference. However, no post-partum measurements were made. Similarly, Gazioglu *et al.* (1970) found no significant change in Tl at 10, 24 and 36 weeks' gestation, the values being no different from those obtained *post partum*. Lehmann (1975) also made serial observation of Tl in 23 subjects and was the first to suggest that this parameter fell during pregnancy. Milne *et al.* (1977a) measured Tl serially in 57 subjects and found

that it decreased significantly from the first trimester until around 27 weeks' gestation with no further fall thereafter (Fig. 3). Interestingly, Tl had not even returned to its first trimester level 12 months *post partum*. Unlike Pecora *et al.* (1963), these workers were unable directly to correlate the fall in Tl with oestrogen status.

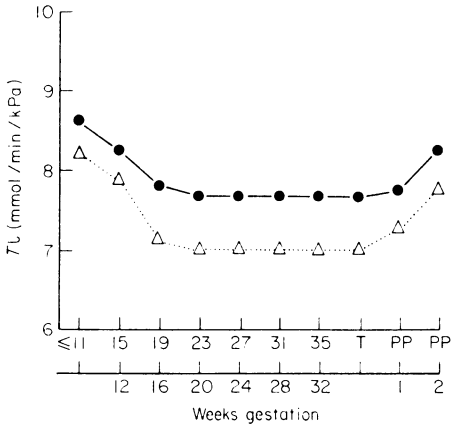

FIG. 3. Pulmonary transfer factor during normal pregnancy and *post partum*. Mean values for 57 subjects. ●——● Corrected for Hb and aveolar volume; △·····△ observed values; T = term; PP = post partum.

In summary, it seems that the increase in ventilation during pregnancy may be offset to some extent by decreased efficiency of gas transfer, although the exact temporal relationship between the two require further investigation.

Pulmonary mechanics

Instinctively, this is the aspect of pulmonary function most obstetricians expect to be altered by the enlarging gravid uterus.

Static lung volumes

There is a plethora of data on this topic stretching from the middle of the nineteenth century to the present day. This is summarized by Woolcock and Read (1972) and more recently by Alaily and Carrol (1978).

The end expiratory volume, functional residual capacity (FRC) and the irreducible residual volume (RV) have consistently been shown to decrease steadily from early in gestation. Figure 4 shows the results of a recent serial study of 61 subjects. A mean decrease in FRC of 0·6 l was demonstrated between

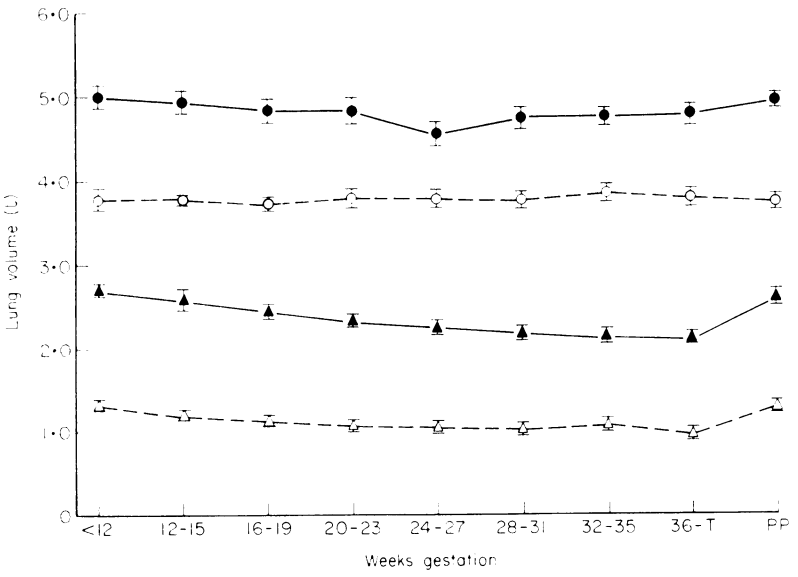

FIG. 4. Static lung volumes during normal pregnancy and *post partum*. Mean values (No. = 61). ●——● Total lung capacity; O----O vital capacity; ▲——▲ functional residual capacity; △----△ residual volume; bar = s.e.mean.

the first trimester and term which agrees well in time-course and magnitude with that shown by Alaily and Carrol (1978) in their study of 38 subjects. Residual volume showed a mean decrease of almost 0·4 litre, also starting from early pregnancy.

Although not a primary lung volume, vital capacity (VC) has been the parameter of pulmonary function most frequently measured during pregnancy and, despite the deficiency of many previous studies, which have variously demonstrated an increase, decrease and no change, it seems unlikely that there is any significant alteration in this parameter throughout pregnancy. Alaily and Carrol (1978) showed no alteration in their study of 38 subjects and the author's own results are in agreement with these (Fig. 4). Similarly, total lung capacity (TLC) remained virtually unaltered.

It is likely that the tendency of the raised diaphragm to reduce TLC is offset by an increase in the antero-posterior and transverse diameters of the chest (Bonica, 1973).

Large airways function

A reduction in resting lung volumes such as occurs during pregnancy will tend to increase the flow resistance of the airways (Briscoe and Du Bois, 1958). Similarly, it has been shown that reduction in P_{A,CO_2}, such as occurs in pregnancy, leads to an increase in airways resistance (Newhouse *et al.*, 1964). Opposing this, the possible direct action of progesterone as a bronchodilator during pregnancy should be considered, for this hormone is known to increase β-adrenergic activity (Raz, Zeigler and Caine, 1973).

Furthermore, the possibility of an effect of the prostaglandins (PGE_2; $PGF_{2\alpha}$) or their metabolites on airways calibre during pregnancy should be considered in view of their known bronchodilator (E_2) and bronchoconstrictor ($F_{2\alpha}$) properties (Fanburg, 1973).

Whenever airways function has been assessed during pregnancy by forced spirometry, no change in function has been noted (e.g. Cameron, Bain and Grant, 1970; Sims, Chamberlain and de Swiet, 1976; Milne *et al.*, 1977c). However, there is disagreement as to what happens to airways resistance (R_{aw}) measured during quiet respiration. This has variably been shown to increase, decrease or remain unchanged during pregnancy. It appears that poor measurement techniques and the failure to normalize for changes in lung volume have both contributed to the conflicting results.

The advent of body plethysmography has greatly improved matters and using this method in a recent study, 30 subjects have had specific conductance (sG_{aw}), the reciprocal of airways resistance normalized for lung volume change, measured serially throughout pregnancy (Table 1). No significant change was demonstrated (Milne *et al.*, 1977c). As with other studies, no significant change was shown in forced expiratory volumes. It would seem likely, however, as discussed earlier, that the constancy of large airways function in pregnancy is a balance between factors tending to increase and those tending to decrease airways resistance.

Small airways function

Obstruction to airflow in the tracheo-bronchial tree was considered for long to be a simple phenomenon easily investigated by the techniques described earlier. However, recent work has shown that airways resistance may be partitioned into that offered by airways greater than 2 mm in diameter (90% of the total) and that offered by those less than 2 mm in diameter (Macklem and Mead, 1967). Thus, there may be extensive disease or dysfunction of these smaller airways before it becomes detectable by the standard methods for assessment of airways function (Hogg, Macklem and Thurlbeck, 1968). Levine *et al.* (1970) have demonstrated that such small airways dysfunction may lead to measurable abnormalities of gas exchange.

It is now possible to investigate the function of these peripheral airways with the use of measurements such as 'closing volume', the lung volume at which the dependent lung zones cease to ventilate owing to small airway closure.

Using the single breath nitrogen technique (Anthonisen *et al.*, 1969), there have been a limited

TABLE 1. Large airways function during normal pregnancy and *post partum*.

	Gestation (weeks)								*Post partum*
	8–11	12–15	16–19	20–23	24–27	28–31	32–35	36–Term	
sG_{aw}($kPa^{-1}sec^{-1}$)*	1·84	1·89	1·94	2·06	1·99	1·99	2·03	2·02	1·96
FEV_1 (litres)	3·12	3·13	3·04	3·07	3·07	3·07	3·05	3·04	3·05
FEV_1/FVC (per cent)	84·0	83·7	82·7	82·4	82·3	82·4	82·4	81·8	84·0
Number of subjects	30	29	30	30	30	30	27	23	30

Paired *t*-tests: in all cases $P > 0{\cdot}1$.

* = $\frac{mmHg^{-1}min^{-1}}{kPa^{-1}sec^{-1}}$ = 7·98.

Key: sG_{aw} = Specific conductance;
FEV_1 = Forced expiratory volume in 1 sec;
FVC = Forced vital capacity.

number of attempts to measure closing volume (CV) in pregnancy. Unfortunately, most studies have in some way been deficient owing to the many factors which influence its determination, e.g. posture, influence of smoking, standardization of the expiratory manoeuvre.

Bevan *et al.* (1974) measured CV once between 36 weeks and term and found that in 50% of their subjects, airways closure occurred during normal tidal ventilation (i.e. above FRC). They suggested that this might lead to impairment of gas exchange in pregnancy although no post-partum measurements were made. Garrard, Littler and Redman (1978) found a linear increase in CV during pregnancy, although by stating that their subjects found difficulty with measurement of vital capacity (VC), the reliability of these findings must be in question.

Craig and Toole (1975) and Baldwin *et al.* (1977), however, found that the point of airways closure was unaltered in pregnancy. There remains a need, therefore, for more detailed investigation of this potentially interesting area of lung function during normal pregnancy.

Dyspnoea during normal pregnancy

It is well known that a significant number of healthy pregnant women complain of dyspnoea at some stage during pregnancy (Thomson and Cohen, 1938; Cugell *et al.*, 1953). The incidence and time-course of the symptom have been documented in a recent study (Milne, Howie and Pack, 1978), (Fig. 5). This showed that almost 50% of subjects complained of dyspnoea before 20 weeks' gestation. Findings such as these have suggested a hormonal rather than a mechanical aetiology for the symptom, although direct evidence for this is scanty. However, in relation to the previously discussed role of progesterone in modifying the respiratory response to changes in P_{CO_2}, Gilbert and Auchincloss (1966) showed that dyspnoeic pregnant subjects were more sensitive to changes in P_{CO_2} than non-dyspnoeic subjects and that they exhibited an inappropriately great ventilatory response which may be experienced as dyspnoea.

These authors also showed that pregnant dyspnoeic subjects had a greater difference between their pregnant and non-pregnant P_{CO_2} levels than did those with no symptoms.

Another theory has been put forward by Lehmann (1975) who suggested that hyperventilation in pregnancy is a secondary response to an oestrogen-mediated fall in gas transfer. He demonstrated that dyspnoeic subjects tended to have lower T_l values in pregnancy than did non-dyspnoeic subjects and postulated that this may in part be responsible for the symptom.

While the exact aetiological mechanism and the temporal relationship of functional change to the development of symptoms still remain to be clarified, there is growing evidence that dyspnoea during pregnancy is in some way related to the individual's adaptation to the inevitable hyperventilation which accompanies the gravid state. It is unlikely that mechanical factors are involved, certainly in the first and second trimesters.

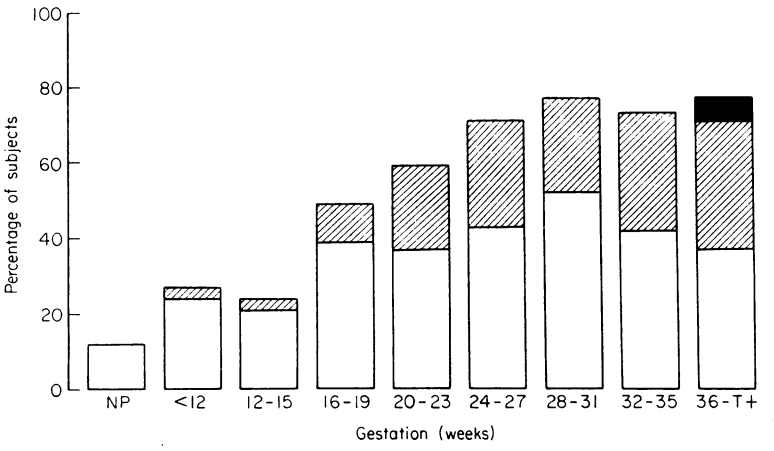

FIG. 5. Incidence, time-course and severity of dyspnoea during normal pregnancy (No. = 62). NP = not pregnant; T = term.
Grade 1 □ = dyspnoea present on climbing hills or more than one flight of stairs;
Grade 2 ▨ = dyspnoea present: (a) on climbing one flight of stairs; (b) walking at an even pace on level ground; (c) during routine performance of housework;
Grade 3 ■ = dyspnoea on slightest exertion or at rest.

Acknowledgments

I would like to thank Dr A. I. Pack for his considerable support and Dr F. Moran and Professor M. C. Macnaughton for their advice. The Scottish Home and Health Department supported the work carried out in the Centre for Respiratory Investigation, Royal Infirmary, Glasgow.

References

ALAILY, A.B. & CARROL, K.B. (1978) Pulmonary ventilation in pregnancy. *British Journal of Obstetrics and Gynaecology*, **85**, 518.

ANTHONISEN, N.R., DANSON, J., ROBERTSON, P.C. & ROSS, W.R.D. (1969) Airway closure as a function of age. *Respiration Physiology*, **8**, 58.

BALDWIN, G.R., MOORTHI, D.S., WHELTON, J.A. & MACDONNELL, K.F. (1977) New lung functions and pregnancy. *American Journal of Obstetrics and Gynecology*, **127**, 235.

BEVAN, D.R., HOLDCROFT, A., LOH, L., MACGREGOR, W.G., O'SULLIVAN, J.C. & SYKES, M.K. (1974) Closing volume and pregnancy. *British Medical Journal*, **1**, 13.

BONICA, J.J. (1973) Maternal respiratory changes during pregnancy and parturition. *Clinical Anesthesiology*, **10**, 1.

BRISCOE, W.A. & DUBOIS, A.B. (1958) The relationship between airway resistance, airway conductance and lung volume in subjects of different age and body size. *Journal of Clinical Investigation*, **37**, 1279.

CAMERON, S.J., BAIN, H.H. & GRANT, I.W.B. (1970) Ventilatory function in pregnancy. *Scottish Medical Journal*, **15**, 243.

CRAIG, D.B. & TOOLE, M.A. (1975) Airway closure in pregnancy. *Canadian Anesthetists' Society Journal*, **22**, 665.

CUGELL, D.W., FRANK, N.R., GAENSLER, E.A. & BADGER, T.L. (1953) Pulmonary function in pregnancy. *American Review of Tuberculosis*, **67**, 1.

ENGLAND, S.J. & FAHRI, L.E. (1976) Fluctuations in alveolar CO_2 and in base excess during the menstrual cycle. *Respiration Physiology*, **26**, 157.

FANBURG, B.L. (1973) Prostaglandins and the lung. *American Review of Respiratory Disease*, **108**, 482.

GARRARD, G.S., LITTLER, W.A. & REDMAN, C.W.G. (1978) Closing volume during normal pregnancy. *Thorax*, **33**, 488.

GAZIOGLU, K., KALTREIDER, N.L., ROSEN, M. & YU, P.N. (1970) Pulmonary function during pregnancy in normal women and in patients with cardio-pulmonary disease. *Thorax*, **25**, 445.

GILBERT, R. & AUCHINCLOSS, J.H. (1966) Dyspnea of pregnancy; clinical and physiological observations. *American Journal of the Medical Sciences*, **252**, 270.

GOODLAND, R.L., REYNOLDS, J.G., MCCOORD, A.B. & POMMERENKE, W.T. (1953) Respiratory and electrolyte effects induced by estrogen and progesterone. *Fertility and Sterility*, **4**, 300.

GUZMAN, C.A. & CAPLAN, R. (1970) Cardiorespiratory response to exercise during pregnancy. *American Journal of Obstetrics and Gynecology*, **108**, 600.

HASSELBALCH, K.A. & GAMMELTOFT, S.A. (1915) Die Neutralitätsiegulatren des gravidens Organismus. *Biochemische Zeitschrift*, **68**, 206.

HOGG, J.C., MACLEM, P.T. & THURLBECK, W.M. (1968) Site and nature of airway obstruction in chronic obstructive lung disease. *New England Journal of Medicine*, **278**, 1355.

HYTTEN, F.E. & LEITCH, I. (1971) *The Physiology of Human Pregnancy*, 2nd edn. Blackwell Scientific Publications, Oxford.

KNUTTGEN, H.G. & EMERSON Jr, K. (1974) Physiological response to pregnancy at rest and during exercise. *Journal of Applied Physiology*, **36**, 549.

KRUMHOLZ, R.A., ECHT, C.R. & ROSS, J.C. (1964) Pulmonary diffusing capacity, capillary blood volume, lung volumes and mechanics of ventilation in early and late pregnancy. *Journal of Laboratory and Clinical Medicine*, **63**, 648.

LEHMANN, V. (1975) Dyspnea in pregnancy. *Journal of Perinatal Medicine*, **3**, 154.

LEVINE, G., HOUSLEY, E., MACLEOD, P. & MACKLEM, P.T. (1970) Gas exchange abnormalities in mild bronchitis and asthma. *New England Journal of Medicine*, **282**, 1277.

LYONS, H.A. & ANTONIO, R. (1959) The sensitivity of the respiratory center in pregnancy and after the administration of progesterone. *Transactions of the Association of American Physicians*, **72**, 173.

LYONS, H.A. & HUANG, C.T. (1968) Therapeutic use of progesterone in alveolar hypoventilation associated with obesity. *American Journal of Medicine*, **44**, 881.

MACKLEM, P.T. & MEAD, J. (1967) Resistance of central and peripheral airways measured by a retrograde catheter. *Journal of Applied Physiology*, **22**, 395.

MILNE, J.A., HOWIE, A.D. & PACK, A.I. (1978) Dyspnoea during normal pregnancy. *British Journal of Obstetrics and Gynaecology*, **85**, 260.

MILNE, J.A., MILLS, R.J., COUTTS, J.R.T., MACNAUGHTON, M.C., MORAN, F. & PACK, A I. (1977a) The effect of human pregnancy on the pulmonary transfer factor for carbon monoxide as measured by the single breath method. *Clinical Science and Molecular Medicine*, **53**, 271.

MILNE, J.A., MILLS, R.J., HOWI, A.D. & PACK, A.I. (1977b) Large airways function during normal pregnancy. *British Journal of Obstetrics and Gynaecology*, **84**, 448.

MILNE, J.A., MILLS, R.J., MORAN, F. & MACNAUGHTON, M.C. (1977c) Maternal gas exchange and acid-base status during normal pregnancy. *Scottish Medical Journal*, **22**, 108. (Abstract.)

MILNE, J.A., PACK, A.I. & COUTTS, J.R.T. (1977d) Gas exchange and acid-base status during ovulatory cycles and those regulated by oral contraceptives. In: *Proceedings of the Society of Endocrinology. Journal of Endocrinology*, **75**, 17p.

NEWHOUSE, M.T., BECKLAKE, M.R., MACKLEM, P.T. & MCGREGOR, M. (1964) Effect of alterations in end-tidal CO_2 tension on flow resistance. *Journal of Applied Physiology*, **19**, 745.

OGILVIE, C.M., FORSTER, R.E., BLAKEMORE, W.S. & MORTON, J.W. (1957) A standardised breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *Journal of Clinical Investigation*, **36**, 1.

PECORA, L.J., PUTNAM, L.R. & BAUM, G.L. (1963) Effects of intravenous estrogens on pulmonary diffusing capacity. *American Journal of Medical Sciences*, **246**, 48.

PERNOLL, M.L., METCALFE, J., KOVACK, P.A., WACHTEL, R. & DUNHAM, M.J. (1975) Ventilation during rest and exercise in pregnancy and post-partum. *Respiration Physiology*, **25**, 295.

PLASS, E.D. & OBERST, F.W. (1938) Respiration and pulmonary ventilation in normal non-pregnant, pregnant and puerperal women. *American Journal of Obstetrics and Gynecology*, **35**, 441.

RAZ, S., ZEIGLER, M. & CAINE, M. (1973) The effect of progesterone on the adrenergic receptors of the urethra. *British Journal of Urology*, **45**, 131.

SIMS, C.D., CHAMBERLAIN, G.V.P. & DE SWIET, M. (1976) Lung function tests in bronchial asthma during and after pregnancy. *British Journal of Obstetrics and Gynaecology*, **83**, 434.

TEMPLETON, A. & KELMAN, G.R. (1976) Maternal blood-gases, (P_{AO2}-Pa_{O2}), physiological shunt and VD/VT in normal pregnancy. *British Journal of Anaesthesia*, **48**, 1001.

THOMSON, K.J. & COHEN. M.E. (1938) Studies on the circulation in pregnancy. II. Vital capacity observations in normal pregnant women. *Surgery, Gynecology and Obstetrics,* **66,** 591.

TYLER, J.M. (1960) The effects of progesterone on the respiration of patients with emphysema and hypercapnia. *Journal of Clinical Investigation,* **39,** 34.

WIDLUND, G. (1945) The cardio-pulmonal function during pregnancy. *Acta obstetrica gynaecologica scandinavica* (*Suppl.* 25), 1.

WOOLCOCK, A.J. & READ, D.J.C. (1972) Respiratory physiology in pregnancy. In: *Human Reproductive Physiology* (Ed. by Shearman, R.P.) 1st edn, p. 639. Blackwell Scientific Publications, Oxford.